

REMARKS

In the Final Office Action dated June 28, 2011, claims 22-24, 30-32, and 35-36 were pending and were rejected on the ground of non-statutory obviousness type double patenting.

Claims 22-24, 30-31, 35-36 stand rejected on the ground of obviousness-type double patenting as allegedly unpatentable over various claims of U.S. Patent 7, 638,618.

Applicants acknowledge that the rejection can be overcome by filing a terminal disclaimer over the commonly owned '618 patent. Applicants will defer responding to the rejection until after the Examiner determines the claimed subject matter to be otherwise allowable.

Claims 22-24, 30-32, and 35-36, i.e., all pending claims, stand rejected on the ground of obviousness-type double patenting as allegedly unpatentable over various claims of U.S. Patent 7,202,059 B2 (hereafter "'059 patent") in view of Dörschug and Schmid et al. (U.S. Patent 5,919,895), and for certain claims, further in view of Badziong et al. (U.S. Patent 5,866,371; hereafter "Badziong").

Applicants respectfully submit that the present claims differ from the referenced claims of the '059 patent in that, for example, the present claims recite a yeast ADH2 promoter and an alpha factor leader sequence, and also recite in claim 36 a yeast cell as a host cell. Applicants respectfully submit that these differences, which have been acknowledged by the Examiner, are not obvious over the combined teachings of the claims of the '059 patent and the cited secondary references. Specifically, the alleged teaching in Dörschug for expression of a mini-proinsulin fusion protein in yeast is a fusion between the precursor sequence of mating factor alpha and mini-proinsulin, not a fusion protein containing hirudin as presently claimed. Additionally, in Badziong, the yeast ADH2 promoter is taught for recombinant expression of

miniproinsulin and hirudin separately; i.e., there is no teaching in Badziong for recombinant expression of a fusion between miniproinsulin and hirudin.

Applicants submitted previously and reassert therein that the Examiner's combination of the elements taught separately in the prior art was improper, especially in light of the unpredictability in the art. In particular, at the time of the invention, it was not predictable that a mini-proinsulin fusion protein having hirudin at the N-terminus could be exported from yeast in good yields; and further that, the present finding that the hirudin-mini-insulin fusion can be expressed and secreted in high yield was unexpected, considering the various attempts documented in the art that only provided a yield below 100 mg/L.

With respect to the unexpected results, the Examiner argues in the Final Action that the claimed nucleic acid and processes "do not recite a limitation requiring a particular yield of fusion protein to be expressed and secreted" (page 10, bottom paragraph of the Final Action). That is, the Examiner contends that the feature which Applicants relied upon (i.e., fusion protein yield that is significantly higher than 100 mg/L) is not recited in the rejected claims. Similarly, on page 12 of the Action, citing MPEP 716.02(d), the Examiner states that "Applicant's alleged 'unexpected results' are not commensurate in scope with the claimed invention".

Applicants respectfully submit that the Examiner's application of the law regarding unexpected results is incorrect. It is true that the law requires the showing of unexpected results to be commensurate in scope with the claimed invention. However, there is no requirement under the law to recite the asserted unexpected result or property *per se* in the claim. See *In re Clemens*, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980); *In re Peterson*, 315 F.3d 1325, 1329-31, 65 USPQ2d 1379, 1382-85 (Fed. Cir. 2003); *In re Grasselli*, 713 F.2d 731, 741, 218 USPQ 769, 777 (Fed. Cir. 1983), all of which are referenced in MPEP 716.02(d).

For example, in *Clemens*, the claims were directed to a process for removing corrosion using a VBC-based ion exchange resin at "elevated temperatures". The unexpected results were provided via comparative tests conducted at 110°C and 130°C where the VBC-based ion exchange resin were shown to be significantly more thermally stable than the prior art ion exchange resin. The Court affirmed the rejection of claims merely reciting "elevated temperatures", because the Court considered the term to encompass temperatures as low as 60°C where the prior art ion exchange resin was known to perform well. However, the Court reversed the rejection of claim 8 which recited a temperature in excess of 100°C. That is, while it is necessary to show unexpected results (i.e., thermal stability of the resin and the resulting effective removal of corrosion) across the claimed range (i.e., the claimed range of elevated temperatures), there is no requirement to recite the unexpected results *per se* (i.e., improved stability of resins and improved efficiency of corrosion removal) in the claims.

Similarly, in the present case, it is not necessary to recite the high yield of insulin in the claims. The high yield is a direct and necessary result of utilizing a yeast ADH2 promoter and a fusion between yeast mating factor alpha, hirudin and mini-proinsulin, preferably in a yeast cell. Therefore, the Examiner's rejection on the premise that the claims do not recite the unexpected results is unsustainable and inconsistent with the law.

With respect to unpredictability, Applicants argued in the previous Response that one would have expected that mis-folding could occur and the stability of the fusion protein could not have been predicted. However, the Examiner contends that this statement is not supported by any evidence, and arguments of counsel cannot take the place of evidence in the record.

Applicants respectfully submit that it was well recognized at the time by those skilled in the art that foreign proteins expressed in yeast could be misfolded, and therefore retained

intracellularly without successful secretion. For example, in a review article on *Foreign Gene Expression in Yeast* (Yeast 8: 423-488, 1992), Romanos et al. describe that folding of secreted proteins occurs in the ER and involves accessory proteins such as BiP and protein disulphide isomerase, and that malformed proteins bind permanently and are retained in the ER. According to Romanos et al., during the secretion of foreign proteins, problems might arise either from saturation of these accessory proteins or from their inability to aid the folding of heterologous proteins. See page 450, right column, first paragraph. Romanos et al. further discuss several reported studies, and conclude that "*attempts to secrete protein fragments or fusions could lead to intracellular accumulation if normal folding and disulfide bond formation cannot take place*" (page 450, right column, second paragraph from the bottom), and that malformed proteins could cause intracellular accumulation of proteins in the secretory pathway, which may also interfere with the secretion of host proteins and result in toxicity (see page 451, left column, first two paragraphs). One of the studies referred to by Romanos et al., namely, Biemans et al., DNA and Cell Biology 10(3): 191-200 (1991), is provided herewith and reports the retention of the large surface protein of hepatitis B virus in the yeast ER, causing the enlargement of the ER. The problem of intercellular accumulation and even degradation of foreign proteins expressed in yeast is also being reported in more recent studies, see, e.g., Agaphonov et al., "*Aggregation and retention of human urokinase type plasminogen activator in the yeast endoplasmic reticulum*" (BMC Molecular Biology 3: 15 (2002)), and Suh et al., "*Yeast flavin-containing monooxygenase is induced by the unfolded protein response*", PNAS 97: 121-126 (2000). Copies of the above-referenced citations are provided together with an Information Disclosure Statement submitted herewith.

Thus, the art supports Applicants' position that one would have expected that mis-

folding could occur and the stability of the fusion protein could not have been predicted. It was simply not predictable at the time of the invention whether fusion proteins containing hirudin or hirudin derivatives at the N-terminus can be exported from yeasts in good yields. Hence, the finding in accordance with the present invention that the hirudin-miniinsulin fusion can be expressed and secreted in high yield was unexpected.

In support of the rejection, the Examiner also states that there is no teaching or suggestion in the prior art of record that would teach away from making the claimed nucleic acid or practicing the claimed processes as written. See page 11 of the Action, top paragraph.

While evidence of teaching away supports a position of unobviousness, there is no requirement for the applicant to provide such evidence in order to establish patentability. On the other hand, Kjeldsen (2000) (submitted in Applicants' last Response dated June 10, 2011) showed that the attempts at the time by those skilled in the art in order to improve the yield were clearly in a different direction from the claimed invention (e.g., by adding a spacer peptide between the kexin2 cleavage site and the N -terminal amino acid of insulin B-chain). The different approaches utilized by others, desires yet failures to improve the yield, and significant unpredictability, when considered together, simply support the patentability of the claimed invention.

In light of the unpredictability in the art, the failures to improve the yield of mini-insulin, and the unexpected results achieved by the present invention, Applicant respectfully submit that the presently claimed process of making a hirudin-min-proinsulin fusion protein, is not obvious over the claims of the '059 patent, taken in view of Dörschug, Schmid and Badziong. Accordingly, the obvious-type double patenting rejection based on the '059 patent, in view of Dörschug, Schmid and Badziong, is overcome.

Conclusion

It is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited

Respectfully submitted,

A handwritten signature in black ink, consisting of stylized, flowing cursive letters that appear to be 'XZ' followed by a long horizontal flourish.

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Enc.: Information Disclosure Statement.